Remarks

Claims 90-101 are under examination after the addition of new claims 95-101 above. Support for new claim 95 is found in the specification at page 17, lines 13-17. New claims 96-101 are supported in claims 25, 26, 28, 29 and 31 as filed and in the specification as filed. Claims 90, 91, 93 and 94 are amended to recite "influenza M2" as supported throughout the specification as filed. The specification is amended to complete the incomplete sentence at page 17, lines 27-29. Support for this amendment is found throughout the specification, particularly in the preceding paragraph at lines 23-26. No new matter is believed added by these amendments and their entry is respectfully requested. Reconsideration and further examination are respectfully requested.

Priority

The Office Action states that an application in which the benefits of an earlier application are desired must contain specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number. Also, the current status of all nonprovisional parent applications referenced should be included.

In this regard applicants have amended the specification to include a claim to priority to

the non-provisional parent application.

Examiner Query

The office action states that Applicants appear to use the term "transmembrane region" in claims 90 and 93 to mean the region of the viral protein encompassing residues 26-43 of the sequence (page 3, lines 21-23). However, in the art, the accepted region of the transmembrane regions appears to comprise residues 25-43. See, e.g., Tosteson et al. (J Membrane Biol 142:117-126, page 118, Figure 1A- of record in the IDS); Watanbe et al. (J Virol 75(12): *5656-5662,* page *5657,* Figure 1); and Black et al. (J Gen Virot, 74:1673-77, page 1673, right column- of record in the IDS). Confirmation that the Applicant is defining the term "transmembrane region"as consisting of residues 26-43 is requested.

Applicants note that the specification and claims are directed to modified influenza M2 polypeptides in which a portion of the transmembrane domain has been deleted. As an example, applicants teach deletion of amino acids 26-43. Applicants agree that it is generally accepted in the art that the transmembrane domain of M2 includes amino acid 25. Thus, applicants teach a deletion of a significant portion of the transmembrane region that retains amino acid 25, and has the functional advantages of the invention. Thus, applicants have treated amino acids 26-43 as the equivalent of the transmembrane domain for the purposes of generating a deletion with the present advantages. However, to clarify the this aspect of the application, applicants herein amend claim 90 to recited deletion of amino acids 26-43. This is believed to address the Examiner's inquiry.

Claim Objections

The Office Action states that Claim 93 is objected to because the claim beings with the

phrase "The method of preparing an M2 antibody..." Because the claim is an independent claim, and because the claimed method has not been previously introduced, the Office Action states that the claim should read, "A method of preparing an M2 antibody..." Appropriate correction is required.

In this regard, applicants have amended the claim as suggested by the office, thus addressing this objection.

Claim Rejections Under 35 USC § 112

Rejections under 35 USC § 112, second paragraph:

Claims 90-94 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In this regard the Office Action further states the following:

> Claim 90 will be treated as representative of the rejected claims. This claim reads on a method "of preparing an M2 antibody" comprising immunizing an animal with a composition comprising a M2 polypeptide and a pharmaceutical carrier. The claims are being rejected because it is unclear what the term "preparing" is intended to convey. As written, the claims read on methods of inducing antibody production in an animal. However, as no further processing or isolation of the antibodies is involved in the claimed inventions, there does not appear to be any "preparation" of the antobodies beyond inducing their creation.

Applicants note that the method as currently written is directed to preparation of an antibody. The Examiner acknowledges that the claims read on antibody production. The skilled person would understand that preparing and producing antibodies in this context have essentially the same meaning in the context of these claims. The skilled person understands that an antibody so prepared can be routinely isolated from the subject of the claim or the antibody so

prepared can remain in the subject. Although both the isolated and *in vivo* antibodies have readily apparent uses, it is noted that the use of the antibody is not relevant since the claims are to a method of making the antibodies and not to a method of using the antibodies. Therefore the requirements of clarity and definiteness are met, and withdrawal of the rejection is respectfully requested.

In keeping with applicants comments above, applicants submit new claim 95, which recites the aspect of the invention in which the antibodies are collected from the subject in which they are prepared.

Claims 93 and 94 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 93 recites the limitation "The method of preparing an M2 antibody, the method comprising..." in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim. It is not clear to which method the claim is referring.

Applicants note that this issue has been addressed with the amendment to claim 93 noted above. Thus, withdrawal of this rejection is respectfully requested.

Rejection under 35 USC § 112, first paragraph:

Claims 90-94 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. In this regard, the Office Action states the

following:

The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims read on methods of raising antibodies to any M2 polypeptide. However, while the Applicant has disclosed the making and use of an M2 polypeptide from the influenza A virus, the Applicant has not disclosed the making and use of the claimed polypeptides from other viruses to make an anti-M2 antibody.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F3d. at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the Genus.

Thus, when a claim covers a genus of inventions the specification must provide written support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed.

In the present case, the Applicant has described the M2 protein, and the transmembrane sequence thereof, for the influenza A virus. E.g., App., pages 1-3. Further, the Applicant has indicated that the claimed invention is drawn to polypeptides from the influenza A protein. See e.g., page 3, lines 28-29. It is noted that the Applicant has nowhere specified that the term M2 polypeptide is limited to polypeptides derived from the M2 protein of the influenza A virus.

It is known in the art that other viruses have M2 proteins, See e.g., Srikiatkhachorn et al., Exp Med 186: 421-32, abstract, and Wagner et al., J Virol 71: 2371-82, abstract each disclosing other viruses with M2 proteins). Because the Applicant has not provided any indication that they were in possession of any other of the claimed M2 polypeptides than those of the influenza A virus, and because the Applicant has not provided any examples of such polypeptides other than those of influenza A, the Applicant has not provided adequate written description support for methods of raising anti-M2 antibodies to any protein other than those of the influenza A virus.

Applicants have amended the claims to clarify their intent to claim methods using "influenza M2" polypeptide. Thus, this rejection in overcome and its withdrawal is requested.

Claim Rejections Under 35 USC § 103

Claims 90, 91, and 93 are rejected under 35 U.S.C 103(a) as allegedly being unpatentable over Kendal et al (U.S. Patent 5,290,686) in view of Black et al. (J Gen Virol- 74: 1673-77- of record in the IDS), Spaete (U.S. Patent 5,474,914). The Office action characterizes this claim as reading on methods of producing monoclonal antibodies to the M2 protein of the influenza virus comprising the administration to a subject a modified M2 polypeptide, wherein the transmembrane domain of the M2 protein has been deleted from the polypeptide, and a pharmaceutical carrier. The Office notes that the polypeptides may also comprise a substitution of the transmembrane region for one or more neutral or hydrophilic amino residues. The Office characterizes the art as follows:

> Kendal teaches a method making and using a vaccine to the influenza A virus comprising recombinantly producing an influenza A M2 protein in a baculovirus/insect cell expression system. See, column 2, lines 53-59, and col.3, lines 14-19. The reference also teaches that M2 protein so produced react with antibodies to the naturally occurring M2 protein, and that such proteins may be used to raise anti-influenza antibodies. See, column 6, lines 16-25, and lines 46-57. Kendal also teaches that the M2 protein is toxic to the insect cell in which it is being expressed. Col.6, lines 7-15. However, the reference does not teach the making and use of M2 polypeptides wherein the transmembrane domain of the M2 protein has been deleted.
>
> Black teaches that the (1) transmembrane region of influenza the M2 protein comprises residues 25-43 of the protein sequence. The reference does not teach the deletion of this region from the protein.
>
> Spaete teaches a method of (1) expressing viral proteins in baculovirus/ insect

cell expression systems. Columns 8-10, and 14-16. While the reference does not identify influenza antigens among the viruses for which the discloses methods may be used, the reference does indicate that the method may be applied to the production of viral proteins generally. Abstract. This, in view of the teaching of Kendal indicating that a baculovirus/ insect cell expression system may be used for M2 polypeptide expression, would have indicated to those in the art that the protein could be express in this system.

Spaete further teaches that, in order to facilitate secretion of the protein, and to prevent transmembrane binding, it is preferable to remove the transmembrane domain of proteins being expressed in the disclosed methods. Col. 5, lines 54-65. Further, the reference also indicates that in the place of the transmembrane region, one may insert other hydrophilic amino residues. Col. 6, lines 14-18. Thus, each of the Kendal and Spaete references provide a reason to combine the references such that the transmembrane domain of the M2 polypeptide is deleted. Spaete to facilitate secretion from the cell, and Kendal, because retention of M2 in the cell is toxic to the cell. It would also be apparent to those in the art that, by removing the limiting factor of protein expression in the Kendal reference (the toxicity of the intracellular M2 in the cell), greater protein expression could be achieved.

It is noted, that Spaete also teaches the use of a fusion of the desired protein signaling for the fusion proteins' secretion. See e.g., column 18, lines 36-49, and claim 1. However, the reference also teaches that the fusion protein preferably comprises processing sites, allowing for the cleaving off of the signaling sequence. Id., at lines 46-49. The use of such processing is known in the art. See e.g., Carter et al., Chapter 13 of *Protein Purification: From Molecular Mechanisms to Large Scale Processes*, American Chemical Society, Washington DC (1990-of record in the IDS filed on April 27, 2000). Thus, while the claims so not exclude embodiments wherein the antibodies are made through the use of a fusion protein of M2 and a secretion signal, the references render obvious embodiments both with and without such a signal.

Because Kendal both teaches the use of the polypeptide as a vaccine, as capable of producing anti-influenza A antibodies, the references teach and suggest the use of the claimed method of making antibodies. Those in the art would have had a reasonable expectation of success in the making of such a protein antigen because Katz et al., (Options for the control of influenza III, pp. 837-43-of record in the IDS) teaches that the antigenically reactive regions of the protein lie in the N-terminal and cytoplasmic C-terminal of the protein, and not in the transmembrane region. See, Katz, page 838, crossover paragraph from page 837). Those in the art would also have had a reasonable expectation in the application of the teachings of Spaete to the protein of Kendal because the art teaches that the desired result (loss of membrane integration) can be achieved in the M2 protein through deletion of at least 6 amino residues from the transmembrane domain. See e.g., Hull et al., J Cell Biol 106: 1489-98, abstract. One skilled in the art would therefore have had a reasonable expectation of success in the making of an immunogenic influenza M2 protein wherein the transmembrane region has been deleted.

It is noted that the references do not teach the exclusion of residues 26-43, rather residues 25-43. However, the claim language does not exclude the additional deletion of

> the N-terminal residue. Further, from the teachings of the above references, it would have been equally obvious to delete only residues 26-43 (leaving the additional residue in place). This is because one skilled in the art would have deemed the deletion of the majority of the transmembrane region sufficient for the expression of a soluble M2 protein.

Applicants respectfully traverse this rejection. None of the cited art discloses a modified M2 polypeptide of any type. None of the art makes any statement that could be construed as a suggestion to make a modified M2 polypeptide. Rather, the cited art is merely a collection of art relating generally to native M2 (Black; and Katz), art relating to the recombinant expression of native M2 (Kendal) and art relating to modification of a special, unrelated class of proteins described as escort proteins (Spaete). There is no guidance provided that would lead one of skill in the art to an M2 construct with the structure as claimed. It is well-established in the law that a combination of references can render a composition obvious only if the combination points to the composition itself, i.e. its structure. See In re Bell, 26 U.S.P.Q.2d, 1529-1533., (Fed. Cir. 1993) and In re Duell, 51 F.3d 1552, 1558 (Fed. Cir. 1995). Thus, the recited combination of references does not support a prima-facie case of obviousness.

Although Kendal teaches that M2 is toxic, it does not provide motivation to address toxicity in the manner of the present invention. In fact, Kendal solves the problem of toxicity in its own, very different manner. Particularly, Kendal uses amantadine-like agents to inhibit the ion-channel activity of M2, thus reducing its toxicity (col. 6, lines 9-15 and Example 4). By providing its own solution to the toxicity issue, Kendal negates any motivation to look to Spaete for a solution to toxicity. Thus, there is no motivation in Kendal to use the teaching of Spaete to

modify M2 in any way, much less in the specific way recited in the present claims.

Black, in addition to describing the transmembrane domain of M2, also appears to contradict Kendal's assertion that M2 is toxic to cells. Black states that M2 protein in the absence of amantadine does not result in cell death (page 1676, L col.,1st para.). In this regard, Black teaches that amantadine targets the transmembrane domain (page 74, R col., 2nd para.), and that there were no differences in cell viability after infection with baculovirus expressing an amantadine-resistant M2 and a baculovirus expressing an amantadine-sensitive M2 (page 1676, L col., 1st para). These teachings of Black remove toxicity as a possible the motivation for modifying M2. As noted above, Kendal itself provides additional reasons not to modify M2.

Spaete is directed to the preparation and use of escort proteins, a special type pf protein with a specific function within cells. Spaete describes only the truncation of CMVgh to remove the transmembrane region (col.5, lines 54-65). Spaete also describes and FGF-R, which has all but the extracellular domain removed (thus, it differs significantly from the type of deletion used in the modified M2 of the invention) (Col. 6, lines 61-67). Also, truncation of FGF-R is described as resulting in escort function (col. 6, lines 65-67), which is totally unrelated, and potentially contradictory, to the goal of the M2 modification as claimed. Furthermore, while Spaete describes its escort-facilitated expression method as applicable to other viruses, it does not implicitly or explicitly suggest application of the transmembrane domain removal to any protein other than CMVgh.

Since Spaete only teaches or suggests a particular motivation (escort function) to remove the transmembrane domain of CMVgh, this cannot be properly extrapolated to other proteins for which a different motivation is relevant. Kendal also does not provide a motivation to delete the transmembrane region of M2, because it provides a different and effective method to reduce toxicity. There is no suggestion and no motivation in Kendal to apply the steps of Spaete to M2. Spaete also provides no motivation to apply its steps to M2, because its sole focus is escort proteins and it teaches nothing and suggests nothing about modification of any other type of protein. Thus, the motivation to make the modified M2 of the invention is lacking in the cited art.

Since motivation to modify M2 is lacking in both Kendal and Spaete, their combination with Black fails to provide the motivational component of a valid obviousness rejection. Thus, withdrawal of this rejection is believed to be merited and is respectfully requested.

Claims 90-93 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Kendal in view of Black and Spaete as applied to claim 90 above, and further in view of Anderson et al. (U.S. Patent 6,180,343). The Office Action further states the following:

> Claim 92 further limits the M2 polypeptide described above to embodiments wherein "all of the deleted amino acids are replaced with from one to six glycine residues." Anderson et al teaches that preferred linkers for fusion proteins include glycine polymers (neutral amino acid), and glycine-serine polymers (a combination of neutral and hydrophilic amino acids). Col. 15, lines 50-59. Because these linkers are known in the art, and because practice of the methods according to the other references above would require some form of connection between the N-terminal and C-terminal regions of the M2 polypeptide, it would have been obvious to use such polymers as linkers to replace the deleted transmembrane region of the M2 protein.

Applicants traverse this rejections on all the grounds recited above. Since there is no motivation in the art to remove transmembrane domain amino acids from M2, there is no motivation to use linkers. Also, a situation calling for linking molecules is not analogous to the present situation where internal amino acids are being deleted, rather than unrelated proteins being joined as is the gist of Anderson. Because Anderson does not fill in the motivation gap that exists in the other cited art as noted above, this rejection is also unsupported, and its withdrawal is requested.

Claim 94 is rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Kendal in view of Black, Spaete, and Anderson as applied to claims 90-93 above, and further in view of Ito et al. (J Virol 65: 5491-98- of record in the IDS). The Office Action further states the following in this regard:

> Claim 94 further limits method of claim 93 to embodiments wherein the M2 polypeptide is derived from the native M2 protein of the influenza virus strain A/Aichi/2/68 (H3N2). The teachings of Kendal, Black, Spaete, and Anderson have been described above. Ito teaches the sequence of the M2 protein of the identified strain. See, page 5494, and 5495 (respectively, the description of Figures 2 (A) and (B), and Figure 2(B)). Because Ito teaches the sequence of the identified strain, because Kendal teaches that the M2 protein is conserved across influenza strains, and because Ito confirms the assertion, those in the art would have been motivated to use the M2 protein of any influenza strain, including the identified strain, as the immunogen in the method taught by Kendal. Thus, it would have been obvious to modify any influenza strain, including the identified strain, as indicated by the additional references.

This rejection is improper for the reasons stated above. The disclosure of the sequence of M2 by Ito does not remedy the failure of the other cited art to motivate the skilled person to modify M2 as described. Thus, withdrawal of this rejection is respectfully requested.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

Enclosed is Credit Card Payment Form PTO-2038 authorizing payment in the amount of $110.00 (one-month extension of time fee). No additional fee is believed due; however, the Commissioner is hereby authorized to charge any additional fees which may be required or to credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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Gwendolyn D. Spratt — 1-26-04

Gwendolyn D. Spratt — Date